UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/889,355	07/08/97	ENGLER H	16930-000811

HM12/0410

WILLIAM M SMITH
TOWNSENT AND TOWNSEND AND CREW
TWO EMBARCADERO CNETER
8TH FLOOR
SAN FRANCISCO CA 94111-3834

EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	12

DATE MAILED: 04/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/889,355	Engler H. et al.
Examiner	**Group Art Unit**
Wilson, Michael C.	1633

☒ Responsive to communication(s) filed on *Jan 19, 2000* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-61* is/are pending in the application.

Of the above, claim(s) *56-61* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-55* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's arguments filed 1-19-00, paper number 11, have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-61 are pending in the instant application.

Applicants argue that the withdrawal of claims 56-61 is improper. Applicants argument is not persuasive because the limitation of administering diagnostic agents was not originally claimed and because administration of diagnostic agents is patentably distinct from administering a therapeutic agent as originally claimed. Diagnostic agents and therapeutic agents have different purposes and different modes of action. Accordingly, withdrawal of claims 56-61 is considered proper. Claims 1-55 under consideration in the instant application.

Priority

1. Applicants state that none of the cited references are dated between the claimed priority date and the actual filing date; therefore, applicants need not address the priority claim at this time. The effective filing date of the instant application remains July 8, 1997.

Claim Rejections - 35 USC § 112

2. Claims 1-55 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons set forth in the office action of 7-9-99, paper number 9.

It is noted that the claims still encompass delivering a therapeutic molecule using the impurity in Formula I and BigCHAP because of the open "comprising" language used in the claims. Example 6 uses BigCHAP containing the impurities to obtain enhanced delivery of DNA which is within the scope of the claims.

The specification does not enable one of skill to determine the impurities which are of use in the instant invention. Example 11 describes using impurities I, II and III isolated from BC BigCHAP. The specification states only two of the impurities demonstrate improved gene transfer and expression (page 29, line 6). Specifically, it appears as though impurity I does not increase gene expression (page 30, line 14). However, it is unclear what impurities I, II and III are because the formula for the impurities is not provided. Therefore, it is unclear which formulas claimed enhance delivery of DNA. In addition, the synthesis of specific compounds as in example 12 does not provide one of skill with the ability to use such a compound to enhance delivery of a compound since some impurities do not improve delivery. Overall, it is unclear which formulas claimed can be used to improve delivery of therapeutic agents.

Applicants argue the generic formula of compounds that enhance DNA delivery as claimed are enabled. Applicants provide Figure 22 of US Application 09/112074 as evidence that impurity I which does not enhance DNA delivery is not within the scope of the generic formula in

applicants claims. Applicants arguments are not persuasive. Figure 22 does not provide the formula for impurity I or correlate the claimed formulas to impurity I in such a way that impurities which enhance DNA delivery could be determined. The specification does not provide adequate guidance for one of skill to determine the structure of impurities that enhance delivery of DNA. Since not all BigCHAP contain impurities that enhance DNA delivery and because it is unclear which impurities enhance DNA delivery or the structure of impurities which enhance DNA delivery, and because it is unclear whether the impurities can be used to enhance DNA delivery, the claims are not enabled.

Claims 1-40 which have therapeutic embodiments are not enabled. As stated previously, the state of the art of gene therapy is unpredictable. The references of record clearly state that it is unpredictable what vector, promoter, mode of delivery and dosage of a gene are required to obtain a therapeutic result (Eck and Wilson, Verma et al., Ross et al. and Marshall all of record). While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels; i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect.

Applicants argue that therapeutic agents are enabled in the instant invention. Applicants argue that the enhanced expression of RB using BigCHAP as in example 6, page 25 enables therapeutic embodiments of the claimed invention. Applicants arguments are not persuasive. Enhanced expression of RB as in example 6 does not indicate that therapeutic levels of expression

are obtained or that therapeutic results occur. The specification does not provide adequate guidance for one of skill to determine the dosage, route of delivery, level of expression, therapeutic effect obtained or target tissue required to obtain a therapeutic effect using RB or any other therapeutic DNA. Given the unpredictability in the art regarding how to obtain a therapeutic effect using gene therapy taken with the guidance provided in the specification, applicants have not enabled delivering any therapeutic DNA as claimed.

Applicants argue that gene therapy clinical trials provide enablement for therapeutic DNA. Applicants argument is not persuasive because of the lack of correlation between expression of a gene product and therapeutic value in the field of gene therapy as taught by Verma et al. of record by stating "Although more than 200 clinical [gene therapy] trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (page 239, column 1, line 16). Thus, it is unpredictable whether gene therapy in clinical trials will result in a therapeutic effect. While clinical trials may provide a possibility of success, based on what was known in the art at the time of filing, one of skill could not predict whether a therapeutic effect could be obtained with a reasonable expectation of success.

Applicants argue the demonstration of delivering marker genes enables the instant invention. Applicants argument is not persuasive. The purpose of the instant invention is to deliver therapeutic compounds (page 1, line 10). Claims 1-40 are directed toward delivering therapeutic agents. The specification does not provide a use for delivering marker genes that is

therapeutic. As the purpose of the specification is to guide the artisan on the making and using of the claimed invention, the artisan reads the claims in light of the teachings in the specification. Thus, the artisan reading the claimed invention in view of the specification would only determine the use of the method of delivering therapeutic agents to be for treating disease. If the Applicants feels other uses for the method of are disclosed in the specification, then the applicants should point to such uses by page and line number.

Applicants argue that methods of administering proteins are enabled. Applicants argument is not persuasive. As stated previously, the specification does not provide adequate guidance regarding what parameters are required to deliver a therapeutic or pharmaceutical protein. It would have required one of skill undue experimentation to determine the parameters required to obtain therapeutic effect using a protein.

Claim Rejections - 35 USC § 102

3. Claims 1, 7, 12, 16, 23, 29, 41-42, 45, 54 and 55 remain rejected under 35 U.S.C. 102(b) as being anticipated by Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) as set forth in the office action of 7-9-99, paper number 9.

Aungst et al. teach the delivery of insulin with various surfactants including BigCHAP to rats (page 230, Figure 1). Applicants state that not all BigCHAP contain impurities that enhance delivery of therapeutic agents. The inventors found the impurities in Calbiochem's BigCHAP and not in Sigma's. Therefore, applicants argue Aungst et al. does not necessarily have the impurities

found in the BigCHAP used by applicants. Applicants arguments are not persuasive because Aungst et al. used Calbiochem's BigCHAP (page 228, column 2, line 17 of Materials). Applicants have not provided any evidence the particular lot of BigCHAP from Calbiochem is the only lot of BigCHAP from Calbiochem that can be used to enhance delivery of therapeutic agents. Therefore, Aungst et al. inherently has the impurities claimed and anticipates the claims as written.

Claim Rejections - 35 USC § 103

4. Claims 1-6, 8, 12-15, 17, 23-26, 30, 39-55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566) for reasons of record set forth in the office action of 7-9-99, paper number 9.

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Aungst et al. do not teach the method of administering a gene to a cell comprising the gene formulated in a buffer comprising a compound of Formula I as described in the claims. However, at the time of filing Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). The formulations in claims 42-53 are impurities also found in BigCHAP as taught by Aungst et al. and are obvious variations of the impurity of Formula I (claim 41) found in BigCHAP. Formula II (claim 54) is an impurity found in BigCHAP as taught by Aungst et al. and the variation in claim 55 is an obvious variant of Formula II.

Applicants argue the obviousness rejection cannot be founded in inherency. The courts have stated otherwise. Reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA). Applicants have failed to distinguish the method or compounds claimed from the method or compounds taught in the art. Applicants claims are not limited to delivery of the impurity alone without BigCHAP; therefore, the cited references provide adequate guidance to deliver a therapeutic agent with BigCHAP from Calbiochem which inherently contains the impurities claimed.

5. Claims 1, 8-10, 12, 17-19, 23 and 30-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566) as applied to claims 1-6, 8, 12-15, 17, 23-26, 30, 39-40 above, and further in view of Wills et al. (1994, Human gene therapy, Vol. 5, pages 1079-1088) for reasons of record set forth in the office action of 7-9-99, paper number 9.

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). Wills et al. disclose the adenovirus encoding p53 for delivery to tumor cells. Applicants repeat the arguments above which are not persuasive as cited above.

6. Claims 1, 8-9, 11-12, 17-18, 20, 23, 30-31, 33 and 37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aungst et al. (1993, Int. J. Pharm., Vol. 53, pages 227-

235) in view of Carson et al. (Sept. 8, 1998, filed Nov. 1, 1994; U.S. Patent, 5,804,566) as applied to claims 1-6, 8, 12-15, 17, 23-26, 30, 39-40 above, and further in view of Takahashi et al. (1991, Proc. Natl. Acad. Sci. USA, Vol. 88, pages 5257-5261).

Aungst et al. teach the delivery of a therapeutic agent with various surfactants including BigCHAP to rats (page 230, Figure 1 and Table 1). Carson et al. disclose the use of surfactants and absorption promoters which facilitate uptake of genes when delivered to the skin or mucosa (column 8, lines 55-63). Takahashi et al. disclose the delivery of a gene encoding full length RB protein into bladder carcinoma (page 5258, column 2, line 8 and line 16). Applicants repeat the arguments above which are not persuasive as cited above.

Claims 21, 22, 35 and 36 appear to be free of the prior art of record.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson